

REMARKS

Claims 27-44 are pending in the application.

Reconsideration of the application is respectfully requested in view of the above amendments and the following remarks. For the Examiner's convenience, Applicants' remarks are presented in the order in which they were raised in the Office Action.

A. Non-Statutory Double Patenting

Claims 27-44 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017.

Claim 27-43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8-12, 14 and 15 of copending Application No. 10/438,313, which is an application for reissue of U.S. Patent No. 5,371,017.

Applicants submit that they will file a terminal disclaimer in the present application to disclaim any term beyond the term of any earlier expiring patent in order to overcome this ground for rejection, after the conflicting claims are found to be allowable, to the extent that the allowed claims conflict under the judicially created doctrine of obviousness type double patenting.

B. Claim Rejections under 35 U.S.C. § 112, First Paragraph

1. Rejection of claims 27-44 for lack of Written Description under 35 U.S.C. § 112, first paragraph

Claims 27-44 remain rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention.

The Examiner has asserted by citation to *Enzo Biochem Inc. v. Gen-Probe Inc.* that the present claims do not satisfy the written description requirement since they do not disclose a representative number of examples.

Applicants respectfully traverse. Applicants again assert that the Examiner has not met the standard for demonstrating a *prima facie* case of written description. The Examiner immediately begins applying the analysis of whether or not the written description has been met. The Examiner must first establish a factual basis for asserting that there is reason to doubt the presumption that the written description has been met. All of the cases cited by the Examiner are applying a written description analysis after the presumption of satisfying the written description has been overcome. If this important step could simply be ignored, then the burden of establishing patentability would simply fall upon the patent application; however, as discussed below when citing *In re Marzocchi*, the burden lies upon the Examiner to establish a *prima facie* case setting forth a reason to doubt and then the analysis of the facts may begin.

Further, satisfaction of the written description requirement is a fact based analysis. Thus, citation to a case as if the case were stating a legal disclosure requirement that must be met in all cases to satisfy the written description requirement cannot establish a *prima facie* case of lack of written description support. The MPEP 2163(a)(1) makes clear that:

“(1) examples are not necessary to support the adequacy of a written description requirement; (2) the written description standard may be met ... even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.’ *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d at 1358, 76 USPQ2d at 1084 (‘The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes’ where the genes were novel combinations of known DNA segments.’)”

Thus, the claimed invention in Inglis was a directed to a modified class of viruses of which there was not a single sequence disclosed in the specification or even referred to in the specification much less multiple examples. Thus, there is no express requirement that a patent with a claim to a virus or viral component must have multiple disclosed examples to comply with the written description requirement.

Since the Examiner's appears to be relying upon the lack of multiple examples of HCV protease variants, etc., for establishing a *prima facie* case of lack of written description support, which the federal circuit has clearly stated is not an absolute requirement, applicants respectfully assert that the Examiner has not established a *prima facie* case of lack of written description support and therefore respectfully request that the written description rejection be withdrawn.

For completeness, the arguments made October 31, 2007 are reiterated here.

Applicants respectfully traverse. As set forth in Section 2163.04 of the MPEP, "[a] written description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971)." The Examiner has not set out a *prima facie* case of lack of written description. The Examiner merely cites to the Federal Circuit generally having held that "a sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs ..." However, this refers to legal conclusions, but compliance with the written description is a fact based inquiry that depends upon what one of skill in the art *at the time of filing* would recognize that the inventor(s) had possession of. For the Federal Circuit cases referred to without citation by the Examiner would need to be evaluated for the similarity or lack thereof to the facts relating to the present claims. At a minimum, this would include a comparison between: (i) the state of the art as of filing of the present application versus the state of the art in the patents at issue in the Federal Circuit cases, (ii) the degree of disclosure in the instant specification versus the disclosure in the patents at issue in the Federal Circuit cases, and (iii) the scope of the pending claims versus the scope of the claims in the patents at issue in the Federal Circuit cases. Without such a rigorous factual analysis, the Examiner has not established a *prima facie* case of lack

of written description and therefore shifted the burden to the applicants to prove they are in compliance with the written description requirement. Citation to the USPTO Written Description Guidelines and Federal Circuit cases cannot supplant this factual analysis otherwise they will be given the effect of a rule of law when the written description analysis is a fact based analysis rather than an application of a rote set of "rules" for compliance.

"[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an Applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Applicants submit that the Specification of the '456 application discloses:

(i) a polynucleotide which encodes an NS3 domain hepatitis C virus protease that corresponds to the HCV NS3 serine protease activity, the protease comprising the entire domain required for NS3 serine protease, and discloses substrates for assaying its activity; and

(ii) a polynucleotide which encodes an NS3 domain hepatitis C virus protease that corresponds to the HCV NS2/3 protease activity, the protease comprising the active site residues of the NS2/3 protease and displaying an autocatalytic activity of the protein fused to a hSOD protein as disclosed in Example 5 of the Specification.

Either activity is sufficient for practicing a "method for assaying compounds for activity against hepatitis C virus."

While the Examiner appears to contend that because Applicants do not maintain that Example 5 of the Specification relates to a HCV NS3 serine protease activity, Applicants are required to rely solely on the NS2/3 protease activity in support of the claimed "NS3 domain HCV

protease." Applicants respectfully disagree. Applicants contend that the "NS3 domain HCV protease" comprises both the NS2/3 protease activity disclosed in Example 5, and the NS3 serine protease activity disclosed *inter alia* in Examples 10 and 11.

- a. The Specification discloses an HCV NS3 domain that has a NS3 serine protease activity.

The Examiner concedes that the specification identifies and recognizes a serine protease activity. Office Action at pages 5-6. The Office Action notes that the specification defines an HCV NS3 domain protease as having termini established "*by expression and processing in an appropriate host* of a DNA construct *encoding the entire NS3 domain.*" (emphasis original). Office Action at page 5.

Applicants submit that the '456 application not only discloses the structure of the NS3 serine protease, it also teaches a method for making it by *in vitro* expression. (Declaration of Dr. Ou, ¶¶ 9-11; Second Declaration of Dr. Weiner, ¶¶ 10-12; page 5, line 11 to page 6, line 4; page 7, line 19 through page 8, line 6; pages 8-9, 37-39, Tables 1 and 2).

Further, the Examiner contends that the publication of Eckart et al. does not support a constructive reduction to practice of a NS3 domain protease that either "comprises" or "consists of" SEQ ID NO:65 in the prophetic Examples 10 and 11 of the specification. According to the Office Action, the various HCV-derived proteins expressed in Eckart et al., whether or not the Ser₁₆₅Gly mutation is present, share the entire NS3 domain and NS4A region, which are sufficient for cleaving at the NS3-NS4 boundary. Office Action, at 12-13. The Examiner suggests that the NS3 protease may not function in the absence of NS4A cofactor, which is absent from "the amino acid sequence of SEQ ID NO:65 or active NS3 domain hepatitis C virus protease truncation analog thereof." Applicants respectfully traverse.

While NS4A has been shown to act as a co-factor with NS3 serine protease, NS3 serine protease cleaves several substrates in the absence of the cofactor NS4A as discussed below. (Declaration of Dr. Ou, ¶¶ 13-18; Second Declaration of Dr. Weiner, ¶¶ 14-19.)

While it is now known that the NS3 serine protease cleaves the HCV polyprotein at multiple sites – NS3/4A, NS4A/4B, NS4B/5A and NS5A/5B, only the NS4B/5A cleavage is dependent on the presence of NS4A. Bartenschlager et al. (J Virol. 68(8):5045-5055 (1994)). Bartenschlager has also shown that the first 211 amino acids of NS3 were sufficient for processing at all *trans* sites.

The NS3 serine protease-mediated cleavages at NS3/4A, NS4A/4B and NS5A/5B are processed efficiently in *trans* by the NS3 serine protease without NS4A.

By using an NS3-5B substrate with an inactivated serine proteinase domain, trans-cleavage was observed at all sites except for the 3/4A site. Deletion of the inactive proteinase domain led to efficient trans-processing at the 3/4A site. Smaller NS4A-4B and NS5A-5B substrates were processed efficiently in *trans*; however, cleavage of an NS4B-5A substrate occurred only when the serine proteinase domain was coexpressed with NS4A.

Abstract, Lin et al., J. Virol. 68(12): 8147-8157 (1994).

Others have reported the same observation that NS4A is not a necessary co-factor for NS3 serine protease activity:

- Sardana et al. (Protein Expression and Purification 16:440-447 (1999)) showed that the NS4A cofactor is essential for "high" proteolytic activity of the NS3 serine protease. (see Abstract). However, Sardana also found that proteolysis at the NS4A/4B junction is carried out at detectable levels by the NS3 serine protease in the absence of NS4A. (Sardana at 443, left col.).
- Vishnuvardhan et al. (FEBS Lett. 402(2-3):209-212 (1997)) showed that a NS3 serine protease representing amino acids 1027–1218 of the HCV polyprotein, and not including any NS4A region, cleaves the NS5A/5B junction in the absence of NS4A. (Figs. 1 and 3). NS4A (amino acids 1658-1712; see Fig. 1) enhances the cleavage but is not essential for it. (Fig. 3). Further, Vishnuvardhan classifies the NS4A/4B cleavage site as "NS4A-independent" cleavage site. (at 211).

- Barbato et al. J. Mol. Biol. (1999) 289, 371-384, at 382, left col. states that "[i]nteraction with the NS4A cofactor is required to perform the cleavages at NS3/NS4A, NS4A/NS4B and NS4B/NS5A junctions but the proteinase in its uncomplexed state is still able to cleave at the NS5A/NS5B boundaries, although with a much lower activity."

In their expert declarations, Drs. Ou and Weiner note that the functionally minimal domain required for activity of the NS3 serine protease is composed of 146 amino acids, residues 1059 to 1204 of the HCV polyprotein. (Yamada et al. Virology 246: 104-112 (1998)). Figure 1 and SEQ ID NO:1 (page 6, line 26 to page 7, line 18) of the '456 application discloses a sequence that encompasses the entire minimal domain of the NS3 serine protease. (Declaration of Dr. Ou, ¶ 18-20; Second Declaration of Dr. Weiner, ¶¶ 19-21.)

It has also been shown that the 146 amino acids long NS3 minimum domain can function by itself as a NS3 serine protease from a structural point of view. Love et al. Cell 87: 331-342 (1996).

Applicants respectfully submit that the specification discloses an "amino acid sequence of SEQ ID NO:65" and "NS3 domain hepatitis C virus protease or active NS3 domain hepatitis C virus protease truncation analog thereof" according to claims 1 and 6 that has HCV NS3 serine protease activity.

As discussed in detail below, under the enablement section, the specification also discloses substrates for "NS3 domain hepatitis C virus protease" such as full length viral polyprotein with the active residues disabled.

Since the specification discloses both a "NS3 domain hepatitis C virus protease" and a substrate therefor, Applicants submit that the specification indicates that the inventors were in possession of "an isolated polynucleotide which encodes an hepatitis C virus (HCV) proteolytic polypeptide, wherein said polypeptide consists essentially of an HCV NS3 domain protease or an

HCV NS3 domain protease active truncation analog” and respectfully request withdrawal of this ground for rejection.

- b. The specification discloses an NS2/NS3 protease activity to those of ordinary skill in the art

The Examiner contends that the specification does not convey the existence of an NS2/NS3 metalloprotease to those of ordinary skill in the art. In particular, the Examiner states that the fusion proteins disclosed in Example 5 of specification are insufficient for HCV-specific proteolysis even though they comprise specific amino acids His-952 and Cys-993 needed for NS2/NS3 metalloprotease cleavage. Office Action at page 3.

It is uncontroverted that the fusion proteins on Example 1 contain 1-151 amino acids of human SOD protein and amino acids 946-1630 of the HCV polyprotein corresponding to the HCV NS3 domain protease sequence of Figure 1; the sequence corresponding to HCV includes C-terminal residues of NS2 and a majority of the NS3 sequence but not including the NS3/4 boundary; and the HCV sequence within this construct includes the putative NS2/3 cleavage site between Leu-1026 and Ala-1027 as well as the catalytic residues His-952 and Cys-993. Office Action at pages 3-4.

The Examiner does not agree that the specification inherently discloses a specific proteolytic activity that is native to the NS2/NS3 metalloprotease, and thus “the issue of whether the specification provides an adequate written disclosure of a claimed assay rests on whether the P600, P500, P300 and P190 proteins of Example 5 provide enough of the art-recognized structure of an HCV NS2/NS3 metalloprotease to permit cleavage at the art-recognized NS2/NS3 cleavage site that is present in each of these proteins.” Office Action at pages 7-8. The Examiner argues that although certain NS2 sequences have been found to be necessary for NS2/NS3 metalloprotease activity (discussing the post-filing truncation studies of Hijikata et al., Grakoui et al., Reed et al., Santolini et al., Pieroni et al., Pallaoro et al. and Thibeault et al.), the fusion proteins of Example 5 lack these necessary NS2 sequences. Office Action at pages 8-11. The Office Action concludes that

the specification fails to disclose or teach the structure of the portion of HCV polypeptide that is sufficient for NS2/NS3 metalloprotease-mediated cleavage at the NS2-NS3 boundary.

Applicants respectfully traverse. Applicants submit that Example 5 relates to the NS2/3 protease and not the NS3 serine protease. Applicants further submit that the observations of Example 5 can be explained by the hSOD fusion portion of the Applicants' constructs being capable of replacing amino acids 898-946 of HCV NS2/3 to create an active protease.

From a review of the specification, one of skill in the art would understand that fusion of heterologous hSOD polypeptide sequence to a truncated NS2/3 protein, that by itself is inactive, restored activity of the NS2/3 protease activity, as discussed in the Declaration of Dr. Ou, ¶¶ 37-39; Second Declaration of Dr. Weiner, ¶¶ 37-39. Fusions with unrelated heterologous proteins are known to restore the activity of inactive proteins or stabilize truncated proteins:

- Fusion of a heterologous polypeptide sequence to a truncated fragment of a protein that by itself is inactive, can restore activity to the fusion protein fragment. A fragment containing the first domain of the CD45 protein lacks phosphatase activity, but fusion of this fragment to maltose-binding protein restores the phosphatase activity. Lorenzo et al., FEBS. 411(2-3):231-5 (1997).
- Fusion with hSOD had been observed to stabilize the HIV protease. (see Pichuanes et al. J. Biol. Chem 265(23), at p.13892, col. 2 (1990))

Since fusion of the NS2/3 fragments containing 299, 513 or 686 residues downstream from residue 946 to the C-terminal of a 151 amino acids long hSOD fragment displayed NS2/3 specific protease activity, as shown in Example 5, one of skill in the art would understand from Example 5 in the specification, that fusion of the heterologous hSOD sequence to the NS2/3 fragments containing the 299, 513 or 686 residues, was sufficient to restore NS2/3 specific protease activity. (Declaration of Dr. Ou, ¶¶ 39-40; Second Declaration of Dr. Weiner, ¶¶ 39-40.)

The crystal structure of the NS2/3 protease has revealed that it is a dimeric protein where each monomer has an amino-terminal subdomain containing two antiparallel alpha-helices (H1 and H2) and an active site is formed by a dimer interface comprising the critical residues for NS2-3 proteolytic activity, His-952 and Glu-972, located in the loop region following helix H2, and Cys-993 located in the b1-b2 loop of the C-terminal subdomain. (Lorenz et al., Nature 442:831-835, at para 3 of left column and para 1 of right column, and Figures 1 and 2, (2006); Declaration of Dr. Ou, ¶41). The NS3 domain sequence of Figure 1 (SEQ ID NO: 70) includes all amino acids involved in dimerization and formation of the active site of the NS2/3 protease.

Applicants note that hSOD ($M_r = 32,000$) is a dimeric protein of 153 residues in each monomer. (Parge et al., Proc. Natl. Acad. Sci. USA 89:6109-6113 (1992).) The N-terminal 151 residues of hSOD are fused to the NS3 domain sequences in Examples 4 and 5 of the Specification.

Further, Applicants submit that stable and active viral protease fusion proteins were known in the art prior to 1991. For example, it was known in 1991 that fusion of heterologous sequences to the N-terminus of proteases does not affect the proteolytic activity of the protease. (Declaration of Dr. Ou, ¶¶ 34-35; Second Declaration of Dr. Weiner, ¶¶ 34-35). Human Immunodeficiency Virus (HIV) proteases remain active when a heterologous sequence is added to either terminus. The fused proteases mediate self-cleavage of viral polyproteins at the correct cleavage sites:

- A fusion protein comprising sequences from chloramphenicol acetyltransferase enzyme and HIV-1 protease is capable of autoprocessing, and mutation of the active site residue results in incorrect cleavage. Montgomery et al., Biochem. Biophys. Res. Comm., 175(3):784-94 (1991).
- An HIV protease fused to the amino or carboxy terminus of bacterial β -galactosidase retains its capacity for specific autoprocessing. Valverde et al., J. Gen. Vir. 73:639-51 (1992)

- c. Cleavage mediated by the fusion proteins of Example 5 correspond to the HCV NS2/NS3 protease cleavage site

The Examiner contends that the calculated molecular mass of the observed cleavage product (24.9 kDa) "is clearly much less than the 34 kD relative molecular mass reported in the specification." Office Action, at page 14. Whereas the specification states that the size of this product is 34 kDa, the Examiner finds the molecular weight of the protein fragment corresponding to a predicted 232 amino acid cleavage product should be 24.9 kDa.

In response, Applicants submit that an anomaly in the estimates of molecular weights of proteins can be explained by a number of causes. Determination of exact molecular weight by SDS-polyacrylamide gel electrophoresis can be unpredictable. While SDS-polyacrylamide gel electrophoresis is often used to estimate molecular weights of proteins by comparing migration of proteins relative to a set of standard markers, it was well-known in 1991 that proteins and proteases do not necessarily migrate on SDS-polyacrylamide gels according to their predicted molecular weight. "[A]bnormalities in SDS binding or protein conformation, large differences in intrinsic protein charge, ... may lead to increased or decreased electrophoretic mobilities; therefore caution is advisable in use of this technique." Proteins: Structural and Molecular Principles. T. Creighton. page 33. (WH Freeman and Co., New York, © 1984). "[D]iscrepancy between apparent relative masses and real molecular weights underlies the uncertainty in deducing molecular masses of membrane-bound proteins from their mobility in electrophoretic gels." Introduction to Protein Structure. Brande C., and Tooze J. page 204 (Garland Publishing, Inc. New York and London © 1991). (Declaration of Dr. Ou, ¶¶ 29-30; Second Declaration of Dr. Weiner, ¶¶ 29-30).

In Example 5, the 34 kDa size is estimated from a Western blot of a SDS-polyacrylamide gel. ("[a] band corresponding to the hSOD fusion partner appeared at a relative molecular weight of about 34." the '456 application;" page 31, line 5 to page 32, line 12)

As discussed in the Declaration of Dr. Ou, ¶ 32; Second Declaration of Dr. Weiner, ¶ 31, several proteases, including a flavivirus NS2/3 protease, are known to migrate according to anomalous molecular weights in SDS-polyacrylamide gel electrophoresis:

- A NS2B-NS3 fusion protein from Dengue virus – a member of the flavivirus family which includes HCV – with a predicted molecular weight of 29.8 kDa displays anomalous migration in SDS-polyacrylamide gel electrophoresis with a higher apparent molecular mass of 37 kDa. Niyomrattanakit P., et al. J. Virol. (2004) 78(24): 13708-13716, at 13711, left column.
- A serine protease with a predicted molecular weight of 24.205 kDa was found to migrate at greater than 26 kDa possibly due to "the presence of bound [protein] defensin, possible posttranslational modifications of the protease, incomplete reduction of the protease during sample preparation or any combination of these possibilities." Hamilton JV et al., Insect Molecular Biology (2002) 11(3): 197–205, at 204, left column.
- The specification itself includes examples showing that estimates of molecular weights of known proteins from SDS-polyacrylamide gel electrophoresis were not precisely according to the predicted theoretical size. For example, the molecular weight of the 151 amino acid hSOD partner by itself was estimated by gel electrophoresis to be about 20 kDa at page 31, lines 15-1, whereas its theoretical size is 16.5 kDa.

One of skill in the art would have understood the "34 kDa" band to correspond to the product of specific cleavage by the NS2/3 protease from the consistent observation of a 34 kDa band reactive to anti-HCV antisera described in Example 5 of the specification of the '456 application, corresponding to the active fusion proteins P300, P500 and P600, but not with the inactive P190 fusion. (Declaration of Dr. Ou, ¶ 33; Second Declaration of Dr. Weiner, ¶ 33.)

One of skill in the art would have understood the inventors of the '456 application to have possession of both species -- a polynucleotide encoding the NS3 serine protease and a polynucleotide encoding the NS2/3 protease -- encompassed by a polynucleotide encoding the

"Hepatitis C Virus NS3 domain protease." Therefore, Applicants respectfully request withdrawal of this ground for rejection under 35 U.S.C. § 112, ¶ 1, for lack of written description.

If the rejection is maintained, Applicants request the Examiner to provide an affidavit under 37 C.F.R. 1.104(d)(2) stating facts within the knowledge of the Examiner as to why the rejection should be maintained. Applicants reserve the right to explain or contradict the assertion with their own affidavits.

2. *Rejection of claims 27-44 for lack of enablement under 35 U.S.C. § 112*

Claims 27-44 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to reasonably provide enablement for the preparation of polynucleotides of the claimed compositions or vectors encoding proteases that cleave at the NS2/3 cleavage site. According to the Office Action, the disclosed NS2 and NS3 domain regions present in the P600, P500, P300 and P190 proteins that Applicant proposes are sufficient for the activity of an HCV NS2/NS3 metalloprotease have been shown by the discoveries of others to actually be insufficient for NS2/NS3 metalloprotease activity.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. (*Genentech Inc. v. NovoNordisk A/S* 108 F.3d 1361, 42 U.S.P.Q.2d 1001 (Fed. Cir. 1997)). Applicants respectfully traverse the rejections and their supporting remarks.

The Examiner in rebutting the arguments of the applicants has asserted that a necessary co-factor, NS4A is missing such that one of skill in the art would be unable to assay protease activities. However, as discussed in the previous Office Action, the co-factor is not necessary for cleavage at all sites. Thus, the use of the polypeptide in its entirety would provide a functional substrate that the claimed fragment would cut therefore providing an assay. The declarations of Dr. Ou and Dr. Weiner completely support this assertion. The Examiner has not responded to the declarations of Dr. Ou and Dr. Weiner. If the Examiner intends to disregard declarations, the Examiner must state with particularity any issues the Examiner has with the declaration. If the

Examiner cannot rebut the factual statements in the Declarations, the applicants respectfully request that the Examiner withdraw the enablement rejection.

For completeness, the arguments made October 31, 2007 are reiterated here.

a. The Examiner has not established a prima facie case of lack of enablement

As with the written description rejection discussed above, the Examiner begins the enablement rejection by asserting that the applicants have not enabled the claimed invention based upon an analysis of what constitutes “undue experimentation.” However, section 2164.04 of the MPEP indicates that “the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557 1563-64 (Fed. Cir. 1994).” The examiner must provide a reason to doubt the objective truth of the statements in the specification. Absent such showing, the burden does not shift to the applicants to prove that the specification is enabled.

b. The specification in light of the art is enabling for the NS2/3 protease

The Examiner states that the specification clearly does not teach how to make a polynucleotide encoding an HCV NS3 domain protease that has NS2/3 protease activity.

Even assuming that the Examiner has established a prima facie case of lack of enablement, as discussed in detail in the previous section and in arguments filed in response to the first Office Action, Example 5 provides a method for making and using polynucleotides encoding the NS2/3 protease by fusion of a peptide having the sequence of Figure 1, or truncation analogs thereof, with a hSOD protein to demonstrate auto-catalytic activity shown in Example 5.

Further, Applicants note that as of the filing date of the parent application, April 4, 1991, vectors comprising polynucleotides that encode fusion of a protein of interest to human superoxide dismutase (hSOD) sequence was an established method of achieving high-level expression of a stable fusion protein. (Declaration of Dr. Ou, ¶¶ 35-36; Second Declaration of Dr. Weiner, ¶¶ 35-

36). The specification of the '456 application discusses the expression from a vector of HIV protease as a fusion with human superoxide dismutase (hSOD) and having autocatalytic proteolysis activity by Pichuantes et al. (Specification, page 2, lines 13-20; Declaration of Dr. Ou, ¶ 35; Second Declaration of Dr. Weiner, ¶ 35).

Prior to 1991, examples of HIV proteases fused with hSOD and showing proteolytic activity for self-cleavage as well as cleavage using viral polyprotein substrates in *trans*, had been reported:

- hSOD-HIV2 protease fusion from bacteria and yeast correctly processes HIV-1 Pr53(gag) polyprotein in *trans* (Fig. 4). Pichuantes et al. J. Biol. Chem 265(23):13890-13898 (1990).
- A fusion protein of HIV1 protease with human superoxide dismutase (hSOD) expressed in yeast displayed correct self-processing, and *trans*-processing of gag-precursor Pr53gag substrate in *in vitro* assays (see Fig. 4, Table 1, Pichuantes et al., Proteins. 6:324-37 (1989)).

Applicants submit that the specification of the '456 application discloses a polynucleotide encoding a polypeptide sequence in Figure 1, which contains the active site residues of the NS2/3 protease, and the cleavage site of the NS2/3 protease. The specification also discloses how to make a NS2/3 protease by fusion with a hSOD partner which was a method that one of skill in the art in 1991 was familiar with. The hSOD fusion displayed autocatalytic cleavage corresponding to the expected NS2/3 cleavage site. Thus, the specification shows how to make and use a polynucleotide encoding an active HCV NS2/3 protease.

The Examiner has asserted that the fusion technology was known for stabilizing proteins which are highly susceptible to protease degradation, but were not known as a means for adding an activity to a protein lacking activity. This assertion is not relevant to the applicants arguments and fails to rebut the teachings in the specification. The hSOD fusion does not “add an activity” to a

protein lacking the activity. The NS2/3 protease taught clearly has the protease activity otherwise adding a fusion protein could not support the activity and even if the fusion protein could "add an activity" it would not add the natural activity of the protein. Clearly, the NS2/3 protease is stabilized by the fusion allowing it to achieve a native fold that displays the NS2/3 protease activity. This is exactly what happens when a fusion protein stabilizes a protein that is highly susceptible to protease which the Examiner acknowledges is a known use of fusion proteins. Proteins that are highly susceptible to protease digestion are susceptible because their native fold is only poorly stable and therefore the protein spends time in partially folded state, which are more accessible and therefore sensitive to proteases. The function of the fusion protein is to stabilize the native state making it less accessible to proteases. One skill in the art would recognize that stabilizing a protein in its native state would improve the activity. Thus, by the Examiner's acknowledgement that fusion proteins were known to stabilize highly susceptible proteins, the Examiner also acknowledges that fusion proteins were known to restore native activity to less stable proteins. Thus, the specifications teaching of an active hSOD fusion provides additional support for the enablement of the NS2/3 metalloprotease.

c. The specification in light of the art is enabling for the NS3 serine protease

Further, Applicants submit that the specification discloses a structure for a polynucleotide encoding the NS3 serine protease and how to find a useful substrate without undue experimentation.

The '456 application not only discloses the structure of a polynucleotide encoding the NS3 serine protease, it also teaches a method for using it for *in vitro* expression. (Declaration of Dr. Ou, ¶¶ 9-11; Second Declaration of Dr. Weiner, ¶¶ 10-12). Page 20, lines 14-16 of the specification discloses full-length polyprotein as a substrate for HCV protease. The specification also discloses use of alternative substrates in the form of "small peptides" (page 20, lines 21-26).

Applicants submit that viral polyprotein substrates for assaying proteases were commonly used in the art at the time of the invention. *See* Declaration of Dr. Ou, ¶ 21; Second

Declaration of Dr. Weiner, ¶ 22. Protease assays using trans-cleavage of viral polyprotein substrates were known in the art at the time of the filing of the invention. Inactivation of the active site in the polyprotein substrate would enable one of skill in the art to assay protease activity in *trans*.

(Declaration of Dr. Ou, ¶ 23; Second Declaration of Dr. Weiner, ¶ 24.)

The following examples show the widespread use of viral polyproteins as substrates for viral proteases prior to 1991:

- Processing of a 250 kDa Sindbis Virus polyprotein substrate (S1234) in vitro by Sindbis Virus protease prepared by in vitro translation. de Groot, et al. The EMBO J. 9(8):2631-2638 (1990):
- Trans-cleavage of a poliovirus capsomer precursor protein by poliovirus proteinase 3C. Nicklin: J. Virol (1988) 62: 4586-4593.
- Trans assay of MLV protease using Gazdar murine sarcoma virus (Gz-MSV) polyprotein Pr65(gag) substrate. Yoshinaka, Proc Natl Acad Sci U S A. (1985) 82(6):1618-1622.
- Trans assay of FeLV protease using Gazdar murine sarcoma virus (Gz-MSV) polyprotein Pr65(gag) substrate. Yoshinaka, J. Virol. (1985) 55(3):870-873.
- Trans assay of BLV protease using MLV polyprotein Pr65(gag) substrate. Yoshinaka *et al.*, J. Virol. (1986) 57(3):826-832.
- The proteinase of human immunodeficiency virus (HIV), expressed in *Escherichia coli*, shows rapid, efficient, and specific cleavage of an in vitro synthesized gag precursor polyprotein. Kräusslich et al., Proc Natl Acad Sci U S A. (1989) 86(3): 807-811.

- Processing of HIV-1 Pr53(gag) polyprotein substrate in trans (Fig. 4) by hSOD-HIV2 protease fusion from bacteria and yeast. Pichuantes et al. J. Biol. Chem 265(23):13890-13898 (1990)
- A fusion protein comprising HIV1 protease fused with human superoxide dismutase (hSOD) expressed in yeast displayed correct self-processing, and trans-processing in vitro of a gag-precursor Pr53gag polyprotein substrate. (see Fig. 4, Table 1, Pichuantes et al., Proteins. 6:324-37 (1989))

Applicants note that a substrate for the serine protease activity in the form of genomic HCV polyprotein is disclosed in page 20, lines 14-16 of the specification. Page 21, lines 4-5 explains that "[i]n the absence of this protease activity, the HCV polyprotein should remain in its unprocessed form." (Declaration of Dr. Ou, ¶ 22; Second Declaration of Dr. Weiner, ¶ 23.)

A method for inactivating the HCV protease activity in a HCV polyprotein by a single point mutation "substituting Ala for Ser121" is disclosed at page 22, line 27 to page 23, line 15 of the specification. One of skill in the art would have understood that this method can be used to inactivate the NS3 serine protease activity of the genomic HCV polyprotein – such that it can then be used as a substrate for testing NS3 serine protease activity in *trans*. (Declaration of Dr. Ou, ¶ 23; Second Declaration of Dr. Weiner, ¶ 24.)

In fact, the method disclosed in the specification was used by Lin et al. who used such a substrate with an inactivated serine proteinase domain to assay trans-cleavage by NS3 serine protease. (Lin et al., J. Virol. 68(12): 8147-8157 (1994)) (Declaration of Dr. Ou, ¶ 24; Second Declaration of Dr. Weiner, ¶ 25.)

Thus, one of skill in the art would understand that the '456 application describes a polynucleotide encoding a NS3 serine protease based on comparison with related flavivirus proteases and identification of critical amino acid residues of the serine triad. One of skill in the art would also understand that a substrate for the NS3 serine protease is disclosed in the '456

application in the form of genomic HCV polyprotein. (Declaration of Dr. Ou, ¶ 25; Second Declaration of Dr. Weiner, ¶ 26.)

Further, one of skill in the art would also understand that a substrate for the NS3 serine protease activity in the absence of NS4A cofactor is disclosed in the '456 application in the form of genomic HCV polyprotein. (Declaration of Dr. Ou, ¶ 25; Second Declaration of Dr. Weiner, ¶ 26.)

The Examiner attempts to rebut this analysis of the specification's disclosure of use of the HCV polyprotein as a substrate by referring to the sentence following page 20, lines 14-16. However, the following sentence begins "For example, ..." Thus the following sentence is giving one particular *example*, which one of skill in the art would clearly understand as not limiting the preceding sentence which teaches use of the HCV polyprotein as a substrate. Thus, the Examiner has not rebutted the enabling disclosure within the specification of using the HCV polyprotein as a substrate, so the NS3 serine protease is enabled.

The '456 application teaches how to make and use a polynucleotide encoding both the NS3 serine protease and the NS2/3 protease encoded by the claimed Hepatitis C Virus NS3 domain protease or a truncation analog thereof, according to independent claims 27 and 37. Therefore, Applicants respectfully request withdrawal of this ground for rejection.

C. Claim Rejections under 35 U.S.C. § 112, Second Paragraph

1. *Rejection of claims 27-44 as being indefinite*

According to the Office Action, claim 23 currently recites, "an NS3 domain hepatitis C virus ... protease truncation analog", but no sequence identifier is present in claim 1 to indicate the metes and bounds of the intended subject matter, such as where the truncation(s) might begin. See Office Action at pages 16-17. For instance, the public cannot determine what is more or less than the "domain" recited in the claims. Although Applicants argued that SEQ ID NO:70 should have the features sufficient for NS2/NS3 protease activity, the Office Action asserts that this sequence

can alternatively, thus ambiguously, be construed to be a active truncation analog of an NS3 protease as well.

The Examiner has asserted that the applicants are arguing a claim limitation that is not present; however, the claims clearly recite an "HCV proteolytic polypeptide" which would clearly indicate that the claimed polypeptide has proteolytic activity toward HCV. All that is required to meet the metes and bounds requirement for definiteness is that one of skill in the art can determine whether they are infringing. As discussed above regarding enablement, the specification provides assays for the proteolytic activities of the polypeptides which can be readily used by one of skill in the art to determine whether their polypeptide is proteolytic toward HCV. The Examiner has not rebutted the declaratory evidence put forward in support of the assays, thus without rebutting the declaratory evidence, the claims are definite as one of skill in the art can simply determine whether they are infringing or not, which is all that is required to satisfy the definiteness rejection. Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 27-44.

For completeness, the arguments made October 31, 2007 are reiterated here.

In response, Applicants submit that independent claims 27 and 37 specify a "HCV proteolytic polypeptide." Thus, one of skill in the art would understand that the "HCV NS3 domain protease truncation analog" need possess a "proteolytic" activity. The NS3 domain of HCV is characterized by the sequence of Figure 1 (SEQ ID NO: 70). The specification describes a truncation analog as: "the sequence may be substantially truncated, particularly at the carboxy terminus, apparently with full retention of protease activity." (page 8, lines 1-3).

As discussed in detail above, the proteins of Example 5 disclose a full length HCV domain protease (P600), truncation analogs that are active (P500, P300), and those that are not (P190). P600 includes all amino acids of Figure 1 (SEQ ID NO: 70). Thus, one of skill in the art would know that a truncation analog of SEQ ID NO: 70 would be a polypeptide that is missing amino acid residues from the full length NS3 domain but retains "proteolytic activity."

Figure 1 and SEQ ID NO:1 (pages 6-7) and SEQ ID NO:70 of the '456 application discloses a sequence that encompasses the entire minimal domain of the NS3 serine protease. (Declaration of Dr. Ou, ¶ 18-20; Second Declaration of Dr. Weiner, ¶¶ 19-21.) Further, SEQ ID NO: 65 which contains residues 1005 to 1204 of the HCV polyprotein, also includes all residues necessary for HCV NS3 serine protease activity.

In their expert declarations, Drs. Ou and Weiner note that the functionally minimal domain required for activity of the NS3 serine protease is composed of 146 amino acids, residues 1059 to 1204 of the HCV polyprotein. (Yamada et al. *Virology* 246: 104-112 (1998)). It has also been shown that the 146 amino acids long NS3 minimum domain can function by itself as a NS3 serine protease from a structural point of view. Love et al. *Cell* 87: 331-342 (1996). Thus, truncation analogs of the sequences of Fig. 1 and SEQ ID NO: 65 that retain NS3 serine protease activity would be readily available to one of skill in the art. Methods for truncation of an expressed amino acid sequence at either end by use of an expression vector and an exonuclease activity was routine in the art and disclosed at page 7, lines 28-31 of the Specification.

By way of response, the Examiner asserts that the applicants have attempted to define the terms asserted to be indefinite by functional limitation which is an admission of indefiniteness. However, even if the terms are defined solely by functional activities, this is not enough for a definiteness rejection. Section 2173.05(g) of the MPEP indicates that, "[f]unctional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210 (CCPA 1971)." Thus, the Examiner's reasoning is not enough to establish a lack of definiteness. Furthermore, the language cited to in the specification may be readily reconciled by one of skill in the art. Page 7, lines 23-26 cited by the Examiner clearly refer to how the protease may be naturally produced, but in no way suggest that the definition is necessarily limited to that which is naturally produced. In fact, it shows that the definition is flexible enough to accommodate different N and C termini. Furthermore, the specification on page 6, lines 22-24 say that the protease is *in* the NS3 domain, not that it *is* the NS3 domain. Thus, neither cited section of the specification rises to the level of an explicit definition and both are actually consistent with the applicants arguments as to definiteness.

Therefore, Applicants respectfully request withdrawal of this ground for rejection under 35 U.S.C. § 112, Second Paragraph for alleged indefiniteness.

2. *Rejection of claims 27-31 as being indefinite*

In addition, the Office Action raises a new ground of rejection of claims 27-31 as indefinite, allegedly necessitate by Applicants' amendment of claim 27 to recite the phrase "consisting essentially of." Office Action at page 14. The Office Action regards this term to be ambiguous and indefinite in the context of HCV protease. The Examiner states that a polynucleotide is a single covalently linked polymer and cannot consist essentially of more than one component.

"By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998).

The Examiner has reiterated his assertions regarding "consists essentially of" applying to ingredients, but has not addressed applicants citation to *AK Steel Corp v. Sollac*, nor has the Examiner addressed the citation to a number of U.S. Patents directed to nucleic acids that use the phrase "consists essentially of" and were not deemed indefinite. Finally, applicants note that the Examiner himself examined U.S. Patent 6,248,577, which includes the claim "3. A purified isolated DNA sequence ***consisting essentially of*** a DNA sequence coding for the protein having the amino acid residue sequence according to claim 1 or for a protein having having substantially the same amino acid sequence and substantially the same HGPRT activity as the protein defined in claim 1." This claim allowed by the Examiner appears to have only one component yet use the phrase "consisting essentially of" as its transition phrase. Thus, applicants respectfully request that the Examiner withdraw the rejection of claims 27-31 or fully address the arguments put forward by the applicants.

For completeness, the arguments made October 31, 2007 are reiterated here.

Applicants respectfully traverse. Applicants submit that claim 27 specifies a “polynucleotide which encodes an hepatitis C virus (HCV) proteolytic polypeptide.” The polypeptide “consists essentially of” an “HCV NS3 domain protease ...” The claim is directed to a polynucleotide that encodes a peptide sequence. A single polynucleotide can encode polypeptide sequences that have a “dominant” component (“HCV NS3 domain protease or an HCV NS3 domain protease active analog”) and other amino acid sequences that do not materially affect the basic and novel properties of the invention may be encoded by the same polynucleotide.

The Examiner has asserted that “consists essentially of” applies only to compositions of matter that have “listed ingredients” and not to a polymer which is covalently bonded nucleotides. However, *AK Steel Corp v. Sollac*, 344 F.3d 1234, 1240-41 (Fed. Cir. 2003) involved claims to a metal coating with a percentage of aluminum. The metal coating has aluminum covalently bonded to other atoms. Thus, a polynucleotide that encodes an HCV NS3 protease covalently linked to a polynucleotide that does not materially affect the basic and novel properties of the invention would fall within the scope of “consists essentially of.” Moreover, the USPTO routinely allows such claims, see, e.g., U.S. Pat. No. 7,282,331, claim 8, U.S. Pat. No. 7,250,507, claim 18, U.S. Pat. No. 7,172,863, claim 22, etc. Therefore, Applicants respectfully request withdrawal of this ground for rejection.

CONCLUSION

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 223002010005. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By /Otis Littlefield/

Otis Littlefield

Registration No.: 48,751

MORRISON & FOERSTER LLP

425 Market Street

San Francisco, California 94105

(415) 268-6846